EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT FOR THE WESTERN DISTRICT OF MISSOURI

JO LEVITT,	)	
Plaintiff,	)	**Case No. 4:06-cv-00818-DW**
v.	)	
MERCK SHARP & DOHME CORP.,	)	
Defendant.	)	

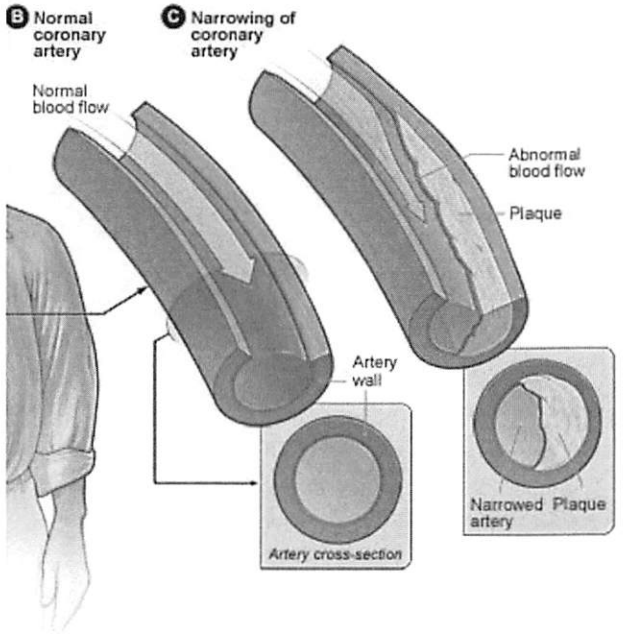
AFFIDVIT OF DR. DAVID EGILMAN, M.D.

1. I am of sound mind and qualified to give the opinions set forth herein.

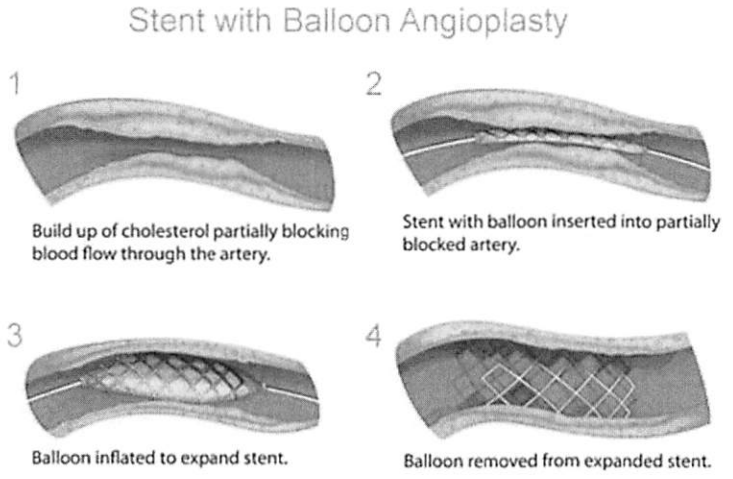
2. I am a medical doctor and board-certified in preventive medicine, occupational medicine and internal medicine. My curriculum vita sets forth more fully my qualifications (Attached as Exhibit A).

3. Acute Coronary Syndrome (ACS) is sudden onset or change in frequency of pain or discomfort usually manifest in the arm, jaw, or neck arm that is caused by insufficient oxygen supply to the heart. This oxygen deficit may be caused by an imbalance in the heart's supply of oxygen. This imbalance may be due to decreased supply that occurs when a cardiac artery develops a clot blocking blood flow to the heart and/or due to an increased oxygen need of the heart ((for example as a result of exercise).

4. The NIH describes Coronary Heart Disease as "a disease in which a waxy substance called plaque builds up inside the coronary arteries. These arteries supply oxygen rich blood to your heart muscle…Over time, plaque can harden or rupture (break open). Hardened plaque narrows the coronary arteries and reduces the flow of oxygen-rich blood to the heart." The NIH goes on to state, "If the flow of oxygen-rich blood to your heart muscle is reduced or blocked, angina or a heart attack can occur. Angina is chest pain or discomfort. It may feel like pressure or squeezing in your chest. The pain also can occur in your shoulders, arms, neck, jaw, or back. Angina pain may even feel like indigestion. A heart attack occurs if the flow of oxygen-rich blood to a section of heart muscle is cut off. If blood flow isn't restored quickly, the section of heart muscle begins to die. Without quick treatment, a heart attack can lead to serious health problems or death." https://www.nhlbi.nih.gov/health/health-topics/topics/cad



5. Mrs. Levitt had a stent procedure to treat her coronary artery disease (CAD). A stent with balloon angioplasty is the insertion of a supportive tube-like structure into a partially blocked artery. The balloon expands the artery and a stent is placed to keep it open.



http://www.webmd.com/heart-disease/ss/slideshow-heart-attack

6. This syndrome of decreased oxygen resulting in pain is called acute coronary syndrome. Some patients who develop ACS go on to suffer a heart attack while others do not. ACS is diagnosed whether or not the patient has a heart attack.

7. All patients with ACS have unstable angina. Vioxx causes ACS. The only study that examined the relationship between ACS and Vioxx, found a statistically significant excess of ACS due to Vioxx-treated patients compared to those who used other Non-steroidal anti-inflammatory (NSAID) drugs Motrin (ibuprofen) and Voltaren (diclofenac). (Aspirin was the first NSAID.)

8. Velentgas et al. found "Vioxx compared to ibuprofen or diclofenac use, the relative risk (RR) of ACS during periods of current rofecoxib use was 1.35 (95% CI 1.09 – 1.68).

Conclusions The incidence of ACS was 1.35 times greater during rofecoxib use than use of ibuprofen or diclofenac." (Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. Velentgas et al. Pharmacoepidemiology and Drug Safety, 2006, 15: 641-652)

9. However at my deposition I provided results for a study that did evaluate unstable angina alone in patients who had taken Vioxx. That study found a statistically significant increase in unstable angina in patients taking Vioxx compared to patients taking diclofenac:

10. Gudbjornsson et al found that "…users of rofecoxib (Vioxx) had the highest IDR of cerebral infarction [2.13 (CI 1.54 –2.97); P<0.001], myocardial infarction [1.77 (CI 1.34 – 2.32); P<0.001] and **hospitalisation for unstable angina pectoris [1.52 (CI 1.01 – 2.30)**; P=0.047]. (Rofecoxib, but not celecoxib, increases the risk, of thromboembolic cardiovascular events in young adults—a nationwide registry-based study, Gudbjornsson et al. Pharmacoepidemiology and Prescription, 2010, 66:619-625)

11. Merck's lawyers speculated without evidence that it was possible that Vioxx lowered the rate of unstable angina while raising the rate of MIs and sudden cardiac death. Ray et al. examined the relative proportion of unstable angina, and CAD disease and found that Vioxx increased the increase in the proportion of unstable angina compared to non-users of NSAIDS. 23.4 % of Vioxx users admitted to hospital for coronary artery disease, experienced unstable angina alone compared to 19.6% for nonusers and this difference was statistically significant p=0.00018.[1]

[1] Wayne A. Ray, PhD; Cristina Varas-Lorenzo, MD, MSc, PhD; Cecilia P. Chung, MD, MPH; Jordi Castellsague, MD, MPH; Katherine T. Murray, MD; C. Michael Stein, MB, ChB; James R. Daugherty, MS; Patrick G. Arbogast,

12. The sine quo none of ACS is pain, shortness of breath, numbness or other symptom caused by a narrowing of the coronary arteries. Narrowing of the coronary arteries is also the cause of a heart attack.

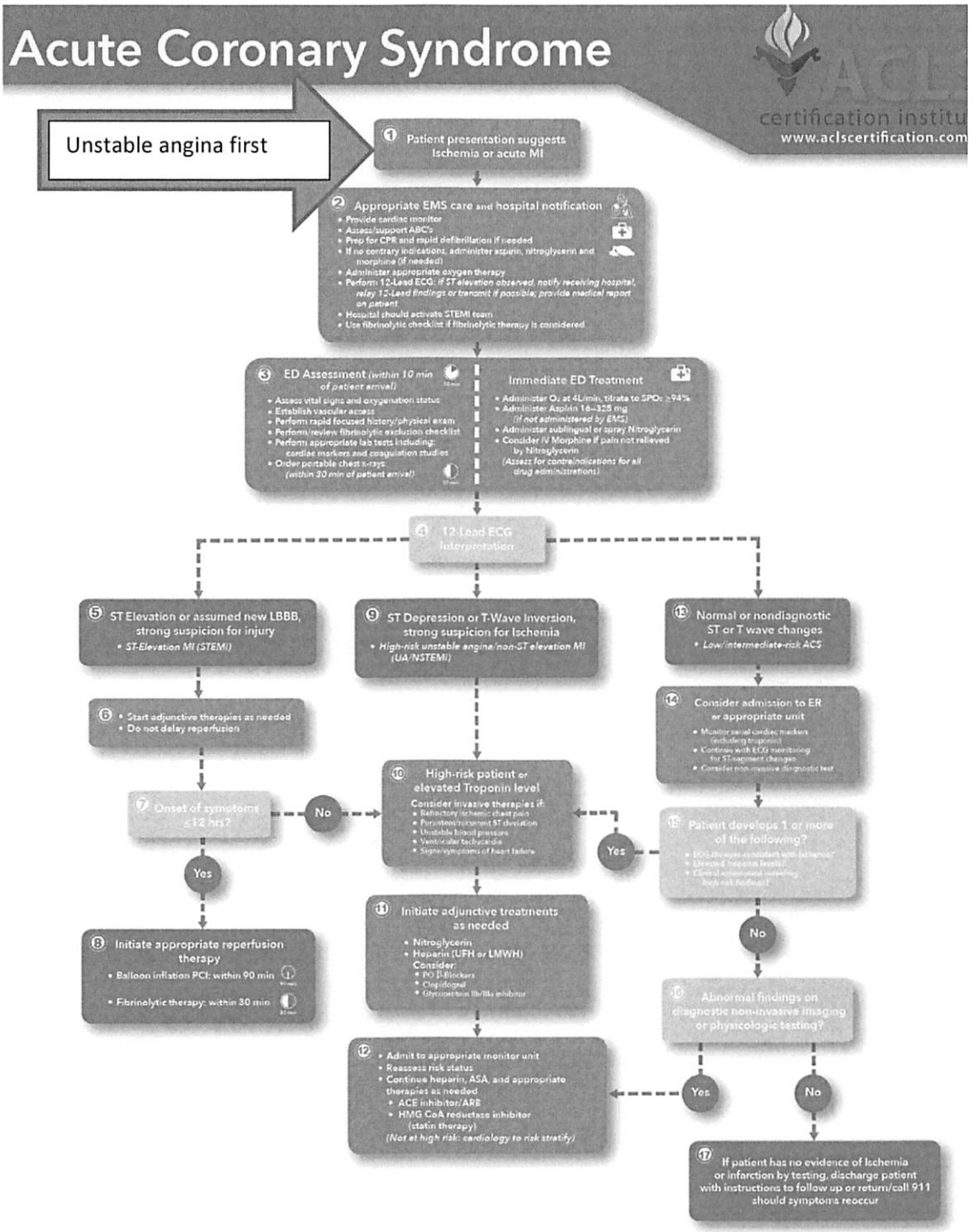
13. ACS is defined as a "set of symptoms" which can result in a heart attack: http://acsalgorithm.net/

Acute Coronary Syndrome

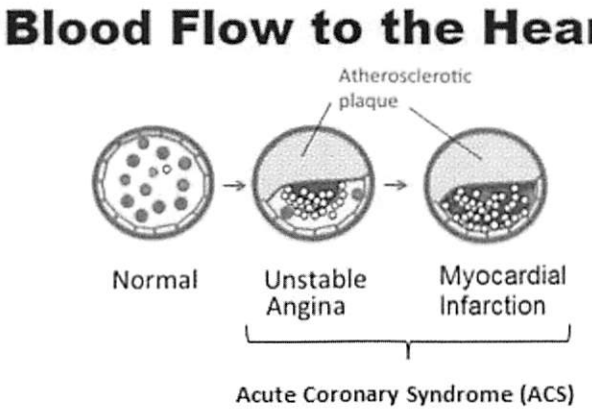
Acute Coronary Syndrome, also known as ACS, is a set of symptoms attributed to obstruction of the coronary arteries. As a result, the most common symptom is chest pain, and at times radiates to the left arm or jaw. ACS typically occurs as a result of ST elevation myocardia infraction, non ST elevation myocardia infraction, or unstable angina. The naming convention for these various types of ACS are based upon they way they appear on the electrocardiogram (ECG). Non ST segment elevation myocardia infraction is known as NSTEMI, where ST segment elevation myocardia infraction is known as STEMI. ACS treatment starts with ACLS

14. This ACS algorithm shows that every patient with ACS has unstable angina first:

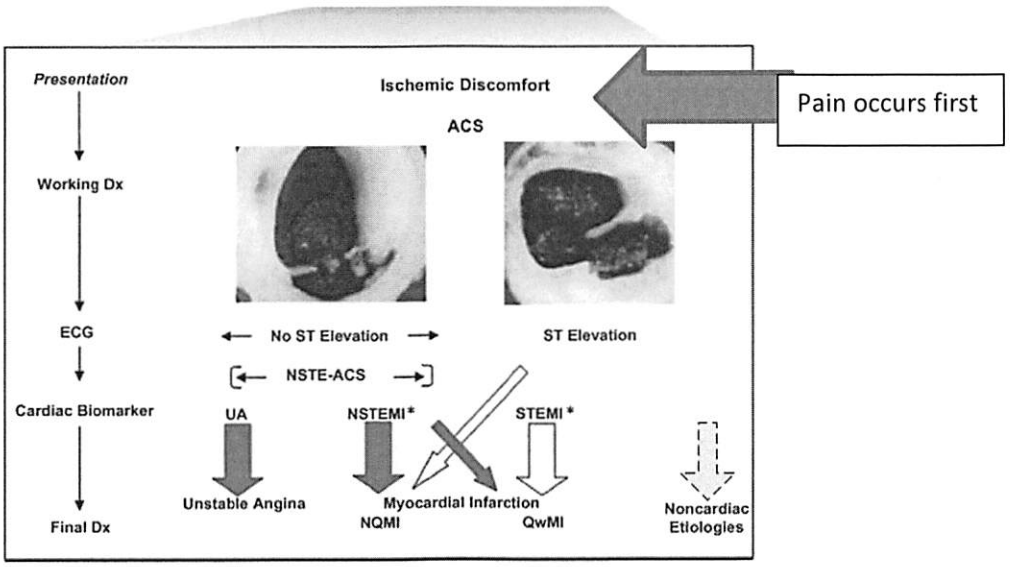
PhD; Luis A. García-Rodríguez, MD, MSc, Cardiovascular Risks of Nonsteroidal Anti-inflammatory Drugs in Patients After Hospitalization for Serious Coronary Heart Disease, Circulation: Cardiovascular Quality and Outcomes v 2 issue 3 pg 155-162, 2009


Acute Coronary Syndrome
certification institu
www.aclscertification.com
Unstable angina first
1 Patient presentation suggests Ischemia or acute MI
2 Appropriate EMS care and hospital notification
• Provide cardiac monitor
• Assess/support ABC's
• Prep for CPR and rapid defibrillation if needed
• If no contrary indications, administer aspirin, nitroglycerin and morphine (if needed)
• Administer appropriate oxygen therapy
• Perform 12-Lead ECG: if ST elevation observed, notify receiving hospital, relay 12-Lead findings or transmit if possible; provide medical report on patient
• Hospital should activate STEMI team
• Use fibrinolytic checklist if fibrinolytic therapy is considered
3 ED Assessment (within 10 min of patient arrival)
• Assess vital signs and oxygenation status
• Establish vascular access
• Perform rapid focused history/physical exam
• Perform/review fibrinolytic exclusion checklist
• Perform appropriate lab tests including: cardiac markers and coagulation studies
• Order portable chest x-rays (within 30 min of patient arrival)
Immediate ED Treatment
• Administer O2 at 4L/min, titrate to SPO2 ≥94%
• Administer Aspirin 16–325 mg (if not administered by EMS)
• Administer sublingual or spray Nitroglycerin
• Consider IV Morphine if pain not relieved by Nitroglycerin
(Assess for contraindications for all drug administrations)
4 12-Lead ECG Interpretation
5 ST Elevation or assumed new LBBB, strong suspicion for injury
• ST-Elevation MI (STEMI)
6 • Start adjunctive therapies as needed
• Do not delay reperfusion
7 Onset of symptoms ≤12 hrs?
No
Yes
8 Initiate appropriate reperfusion therapy
• Balloon inflation PCI: within 90 min
• Fibrinolytic therapy: within 30 min
9 ST Depression or T-Wave Inversion, strong suspicion for Ischemia
• High-risk unstable angina/non-ST elevation MI (UA/NSTEMI)
10 High-risk patient or elevated Troponin level
Consider invasive therapies if:
• Refractory ischemic chest pain
• Persistent/recurrent ST deviation
• Unstable blood pressure
• Ventricular tachycardia
• Signs/symptoms of heart failure
11 Initiate adjunctive treatments as needed
• Nitroglycerin
• Heparin (UFH or LMWH)
Consider:
• PO β-Blockers
• Clopidogrel
• Glycoprotein IIb/IIIa inhibitor
12 • Admit to appropriate monitor unit
• Reassess risk status
• Continue heparin, ASA, and appropriate therapies as needed
• ACE inhibitor/ARB
• HMG CoA reductase inhibitor (statin therapy)
(Not at high risk: cardiology to risk stratify)
13 Normal or nondiagnostic ST or T wave changes
• Low/intermediate-risk ACS
14 Consider admission to ER or appropriate unit
• Monitor serial cardiac markers (including troponin)
• Continue with ECG monitoring for ST-segment changes
• Consider non-invasive diagnostic test
15 Patient develops 1 or more of the following?
• ECG changes consistent with ischemia
• Elevated troponin levels
• Clinical circumstances indicating high risk features
Yes
No
16 Abnormal findings on diagnostic non-invasive imaging or physiologic testing?
Yes
No
17 If patient has no evidence of ischemia or infarction by testing, discharge patient with instructions to follow up or return/call 911 should symptoms reoccur

Unstable angina and heart attack have the same cause



Unstable angina **precedes** heart attack



15. Unstable angina most often presents as either chest, arm or jaw pain. A study of unstable angina will not enumerate the location of the pain. Merck's argument is that if unstable angina is elevated I cannot say that the jaw pain presentation is elevated without analyzing the data for "jaw pain." But unstable angina is diagnosed by clinical history and EKG changes whatever the pain location just as ACS is present if the presentation is Unstable angina, MI or sudden death.

16. The final diagnosis of patients who have ACS may be recorded as unstable angina, heart attack (myocardial infarction) or sudden cardiac death. But in all cases the disease process that causes the pain and/or heart attack is the same and in all cases patients diagnosed with ACS have pain (as described above).

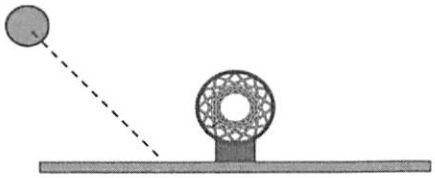
17. ACS is not a combination of "different fruits"; it is the result of a seed that may produce a stem **AND** a flower (unstable angina and a heart attack) or just a stem (unstable angina). The seed is a shortage of oxygen to the heart. The same seed produces the stem and/or the flower.

18. Given that it's time for the NCAA March Madness tournament, an even more apt analogy may be taken from basketball. When a layup is attempted in basketball, sometimes the ball hits the backboard and does not go in, sometimes it hits and goes in, and other times it goes in without hitting the backboard at all. However, all three scenarios are caused by shooting the ball. In this scenario, unstable angina is analogous to the basketball hitting the backboard during a layup attempt; the ball going through the basket is analogous to a heart attack. The same three outcomes are possible: 1) An unstable angina may occur without a heart attack (the ball hits the backboard, but does not go into the basket); 2) an unstable angina may occur followed by a heart attack (the ball hits the backboard and goes into the basket); or 3) a heart attack may occur without unstable angina (the ball goes directly into the basket without hitting the backboard).

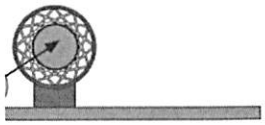
    In the case of ACS, unstable angina sometimes occurs without myocardial infarction and sometimes myocardial infarction occurs without unstable angina. Most often they occur together. Regardless, all three conditions are caused by Vioxx and all three are symptoms of the same disease:

19.

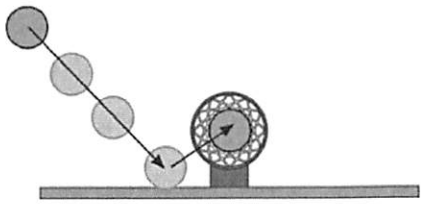
Unstable angina is analogous to the basketball hitting the backboard during a layup attempt



The ball going through the basket is analogous to a heart attack

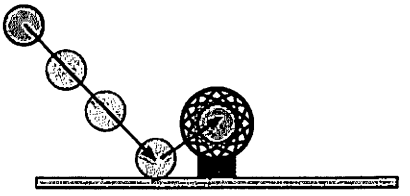


The ball usually hits the backboard (unstable angina) before going through the basket (heart attack)



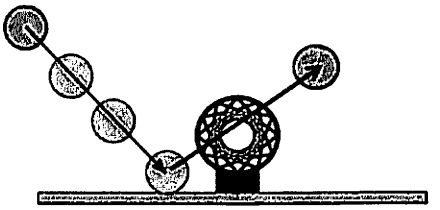
If a shot hit the back board (angina) and went through the net (heart attack) Merck did not count the back board hit (angina). Merck recorded this as MI only -- not MI and unstable angina

The ball usually hits the backboard (unstable angina) before going through the basket (heart attack)



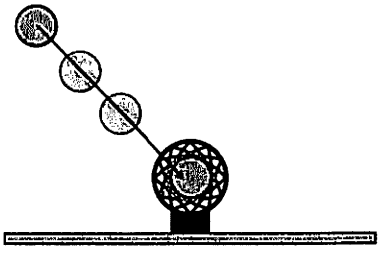
If a shot hits the back board and goes through the net Merck did not count the back board hit. Merck recorded this as an MI only not MI and unstable angina

Sometimes unstable angina does not lead to a heart attack



This is counted as unstable angina

And rarely a heart attack occurs without unstable angina



Merck counted this as a sudden death

Condition	Coded as	ACS	Unstable angina
Unstable Angina →	Unstable Angina	YES	YES
Unstable Angina → MI	MI	YES	YES
Unstable Angina → MI → Cardiac Death	Cardiac Death	YES	YES

20. None of Merck's studies separately recorded all unstable angina cases. If a patient had unstable angina and a heart attack Merck discarded the "unstable angina" diagnosis and recorded the case as a heart attack only. Merck altered the patient case report forms and erased heart related diagnoses from the case report records of patients who had taken Vioxx. Therefore without access to actual patient records there is no way to analyze Merck studies to compare rates of unstable angina alone. Merck has produced only a few case report forms and no complete medical records.

21. Defense witness Dr. Vaughn reports cases of unstable angina that did not result in heart attack in his report. However his "analysis" excludes all patients who had unstable angina who also had heart attacks. Most, if not all of these patients, also had unstable angina. However, as noted above, Merck discarded this data and did not report it in their published papers.

22. All witnesses for both sides agree that Mrs. Levitt had ACS:

23. Dr. Rosamond:

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"I said that she -- or meant to say she didn't have a myocardial infarction. **But a heart attack is a lay term that people apply to any acute coronary syndrome presentation. And she did have that.** And I remember that when I did her heart cath, it appeared to me that she had active thrombus in her LAD. So to me that's a heart attack, but it's not an infarction."

24. Dr Schapira:

"After careful review of these materials, I do not feel that any changes to my original report are necessary with the exception of a wording change on page 7, wherein I refer to an "acute myocardial infarction" and feel that this is more properly stated as "**acute coronary syndrome.**"

25. Dr. Vaughn agrees with my diagnosis of ACS, writing that Mrs. Levitt…

"Prior to **her acute coronary syndrome** episode in March 2000" (pg 72); "Further, the data with respect to any association between Vioxx and the **specific syndrome suffered by Ms. Levitt – unstable angina / acute coronary syndrome** – are weak." (pg 83); and "Further, **given the clinical profile of Ms. Levitt and the circumstances of her acute coronary syndrome,** there is no reason to implicate Vioxx as causative of her event." (pg 90)

26. Defense witness Dr. Pratt also agrees. In fact the lawyers asked their witness, Dr. Pratt, to assume that Mrs. Levitt suffered from Acute Coronary Syndrome in his assignment:

"I have been asked to address the question of whether Mrs. Levitt suffered a myocardial infarction in 2000 and whether there is any **relationship between Mrs. Levitt's acute coronary syndrome** and her use of Vioxx®." (First sentence of report) "…there is no relationship between the **acute coronary syndrome that Mrs. Levitt did experience** and her treatment with Vioxx;" (pg 7) "**Mrs. Levitt was hospitalized in March 2000 and treated for acute coronary syndrome.**" (pg 7), "Levitt took Vioxx for less than seven months **before her acute coronary syndrome event on 3/9/00,"**(pg7).

27. Merck generalizes my specific criticism of Merck's use of the APTC composite measure to a criticism of ACS by selectively citing two sentences in the middle of a paragraph:

> **The APTC endpoint groups together and "includes CV, hemorrhagic, and unknown deaths; nonfatal myocardial infarctions; and nonfatal strokes." Thus, the meta-analysis could not detect risk in a specific CV subcategory, since any risk in one category might be offset by lack of risk in another subcategory.**

28. The complete paragraph reveals that Merck's selective quotation is misleading because it omitted the explanation for my criticism of this particular composite outcome which I explained in the next sentence of the same paragraph:

> Despite the excessive risk in the myocardial infarction endpoint for VIGOR, Merck's published 2001 meta-analysis, ostensibly designed to investigate the risk of MI's in all RCT's, obscured the risk of MI by using the APTC (Antiplatelet Trialists' Collaboration) endpoint. The APTC endpoint groups together and "includes CV, hemorrhagic, and unknown deaths; nonfatal myocardial infarctions; and nonfatal strokes." Thus, the meta-analysis could not detect risk in a specific CV subcategory, since any risk in one category might be offset by lack of risk in another subcategory. **Given the VIGOR results, Merck should have been looking specifically at MI and related events and should have presented these categories separately.** The main adverse effects in VIGOR were MI and related events. Conflating the effect measure with acute CNS effects obscured the acute and sub-chronic cardiac thrombotic events. In addition it was misleading to exclude hypertension and CHF from the CV event analysis. Hypertension causes CNS and cardiac adverse events and MIs can present as CHF. The retrospective removal of CHF from the SOP caused the adjudicated analysis to be biased. This was particularly bad because CHF was removed by Dr. Reicin after she was unblinded, after the concern for CV effects of Vioxx became known. Another example of the problem of unbliended [sic] researchers occurred when Eliav Barr, moved 6 MIs from the CV category to the unknown category in an early Alzheimer's data re-analysis after he became aware of the Vioxx CV problem. If all the MIs were eliminated no matter what the exposure the problem would

disappear or the difference would not be statistically significant, regardless of the exposure.

29. Merck intentionally chose the APTC composite measure because it conflated bleeding and clotting events. Merck knew that Vioxx would reduce bleeds and increase clots (resulting in heart attacks) and chose this measure to hide the adverse clotting effects of this drug. As I noted in my report Merck selected the APTC composite measure precisely to hide the thrombotic effects of Vioxx:

> Dr. Alice Reicin, Vice-President of clinical research, and Deborah Shapiro, the VIOXX project statistician, created a list of outcome measures that could be used for a planned meta-analysis which would be published in response to the VIGOR results. The list compares the pros and cons of three different outcome measures that MERCK could use to analyze the results in this meta-analysis: 1) The original 1998 cardiovascular SOP, which was limited to "confirmed arterial and venous thromboembolic CV" [*sic] events, the "APTC endpoint," which included both thrombotic and bleeding events including GI bleed and 3) a modified APTC which excluded bleeding events. (MRK-NJ0363443-5)
>
> The memo lists a comparison of pros and cons for each outcome measure. The pros for the second option, the APTC definition of event, Reicin wrote, "The pros for the APTC endpoint included: Endpoint definition which is accepted by authorities worldwide, Ease of bench marking our results to other studies, does not mix arterial and venous and Only uses 'hard' endpoints--especially attractive for the interim analysis which will rely on events which have not yet been adjudicated**". Reicin wrote that the cons of the APTC, "Include[s] 'bleeding' endpoints which mixes risk/benefit (could be seen as a pro since this could work in our favor)."** [Emphasis added] (MRK-NJ0363443) pg 32-33

30. ACS is not a composite outcome; this is clearly shown by the fact that all experts in this case diagnose Mrs. Levitt with ACS. ACS is a diagnosis or disease by itself. In addition the APTC endpoint I criticized excluded (did not record) unstable angina cases.

DRAFT Data Analysis Plan for FDA Request of Special Safety Analyses for AD Studies9

Adjudication Committee Categories for Cardiovascular Events	Confirmed Thrombotic Event	Confirmed APTC† Event
Thrombotic Events		
Cardiac Events		
Acute MI	√	√
Fatal: Acute MI	√	√
Unstable Angina Pectoris	√	
Sudden and/or Unexplained Death	√	√
Resuscitated Cardiac Arrest	√	√
Cardiac Thrombus	√	

31. Merck's original plan for reporting results included grouping unstable angina and heart attacks:

3. Thrombotic Cardiovascular Serious Adverse Experiences in the VIGOR Study (Cont.)

Table 14

Summary of Thrombotic Cardiovascular Serious Adverse Experiences Referred for Adjudication
VIGOR Study in Patients With Rheumatoid Arthritis

	Rofecoxib (N=4047)†		Naproxen (N=4029)‡	
	n	(%)	n	(%)
Patients with one or more thrombotic cardiovascular serious adverse experiences	55	(1.4)	30	(0.7)
Coronary Artery Disease Terms				
Cardiac Arrest	1	(0.0)	0	(0.0)
Ventricular Fibrillation	1	(0.0)	0	(0.0)
Acute Myocardial Infarction	4	(0.1)	4	(0.1)
Myocardial Infarction	14	(0.3)	4	(0.1)
Non-Q-Wave Myocardial Infarction	1	(0.0)	0	(0.0)
Coronary Artery Occlusion	1	(0.0)	0	(0.0)
Unstable Angina	5	(0.1)	1	(0.0)
Angina Pectoris	0	(0.0)	6	(0.1)
Ischemic Heart Disease	1	(0.0)	1	(0.0)
Coronary Artery Disease	2	(0.0)	2	(0.0)
Cerebrovascular Disease Terms				
Carotid Artery Obstruction	2	(0.0)	0	(0.0)
Cerebral Infarction	0	(0.0)	1	(0.0)
Cerebrovascular Accident	12	(0.3)	4	(0.1)
Cerebrovascular Disorder	1	(0.0)	0	(0.0)
Intracranial Hemorrhage	0	(0.0)	2	(0.0)
Paresis	1	(0.0)	0	(0.0)
Transient Ischemic Attack	2	(0.0)	3	(0.1)
Peripheral and Other Vascular Disease Terms				
Arterial Embolism	1	(0.0)	0	(0.0)
Arterial Occlusion	1	(0.0)	0	(0.0)
Deep Venous Thrombosis	4	(0.1)	1	(0.0)
Femoral Artery Occlusion	0	(0.0)	1	(0.0)
Peripheral Vascular Disorder	1	(0.0)	0	(0.0)
Venous Insufficiency	0	(0.0)	1	(0.0)

† These 4047 patients represented 2695 patient-years at risk.
‡ These 4029 patients represented 2696 patient-years at risk.
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[Attachment 31

Uterine Hemorrhage	3	(0.1)	2 (0.0)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a body system. The same patient may appear in different body systems.

32. Under this grouping a patient who had unstable angina and a heart attack would be adjudicated to a heart attack and be recorded once as a heart attack and the angina diagnosis would not be recorded because, "Although a patient may have had two or more clinical adverse experiences the patient is counted only once within a body system."

33. Merck changed the combined outcome measure to APTC from cardiovascular thrombotic events. APTC excluded angina; therefore Merck did not report angina separately:

Rofecoxib VIGOR
CV Events Analysis

39

3. **Thrombotic Cardiovascular Serious Adverse Experiences in the VIGOR Study (Cont.)**

Table 11 (Cont.)

Analyses of Cardiovascular Events in the VIGOR Study Using Endpoint Definitions Standard in Large Antiplatelet Trials

Event Category	Treatment Group	N	Number of Patients With Events	PYR[a]	Rates[b]	Relative Risk[c] Estimate	95% CI
Aspirin Not Indicated[d]							
Cardiovascular deaths[e], myocardial infarction, stroke[f]	Rofecoxib	3877	20	2593	0.77		
	Naproxen	3873	14	2596	0.54	0.70	(0.35, 1.38)
Cardiovascular deaths[e]	Rofecoxib	3877	6	2594	0.23		
	Naproxen	3873	5	2597	0.19	0.83	(0.25, 2.73)
Myocardial infarction	Rofecoxib	3877	9	2594	0.35		
	Naproxen	3873	4	2597	0.15	0.44	(0.14, 1.44)
Stroke[f]	Rofecoxib	3877	8	2593	0.31		
	Naproxen	3873	6	2597	0.23	0.75	(0.26, 2.15)

[a] Patient-years at risk.
[b] Per 100 PYR.
[c] Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
[e] Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal GI bleeding episode
[f] Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes
[d] "Aspirin Indicated" patients are patients with past medical histories of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions). [20] "Aspirin Not Indicated" patients are patients without a past medical history of these conditions.

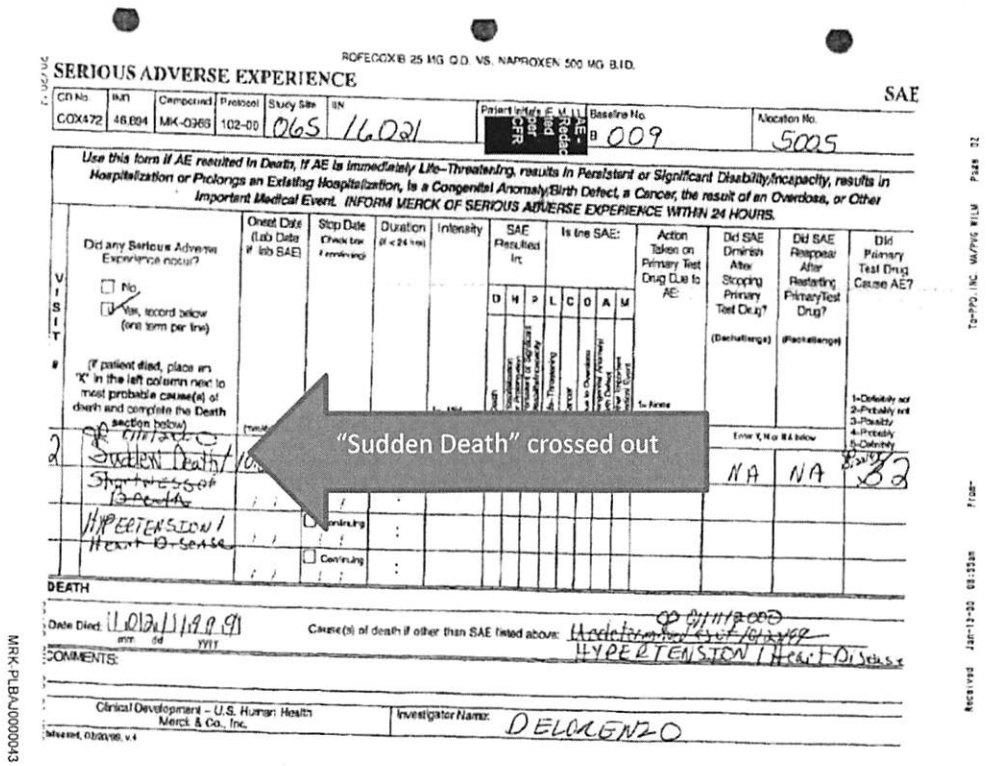
[Attachment 3]

No angina

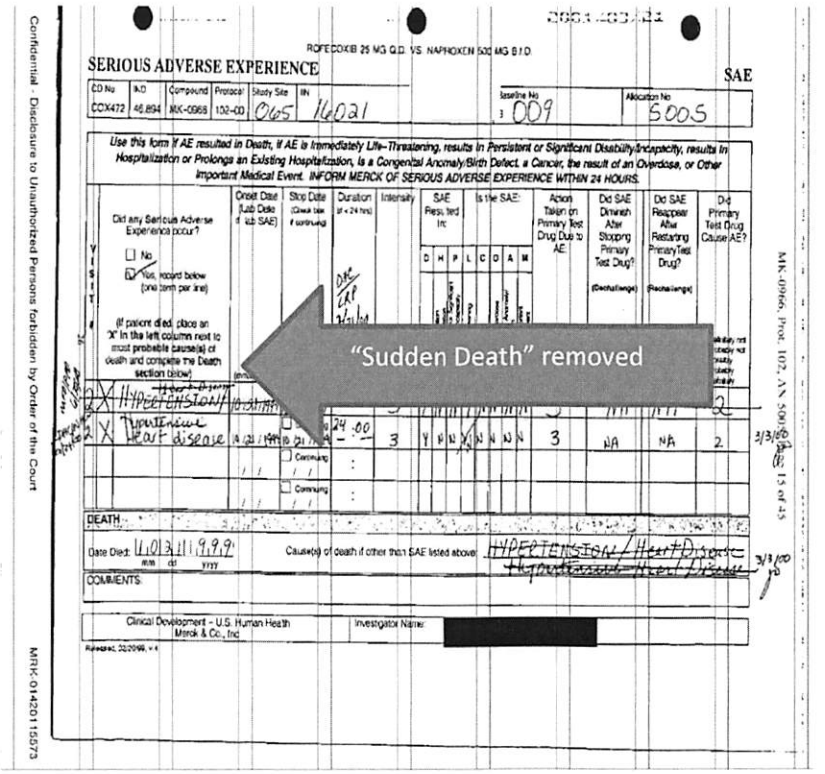
34. Since Merck used some formal, some ad hoc informal, and some adjudicated data, it is impossible to analyze the Merck data bases for the "unstable angina" category. This would require evaluation and coding of all the patient medical records, and Merck never produced these.

35. I cited an example of Merck manipulation of study clinical report forms, which is another form of data, that shows that Merck manipulated patient diagnoses by manipulating cardiac diagnoses. Therefore, a review of actual records would be required to assess the incidence of unstable angina:

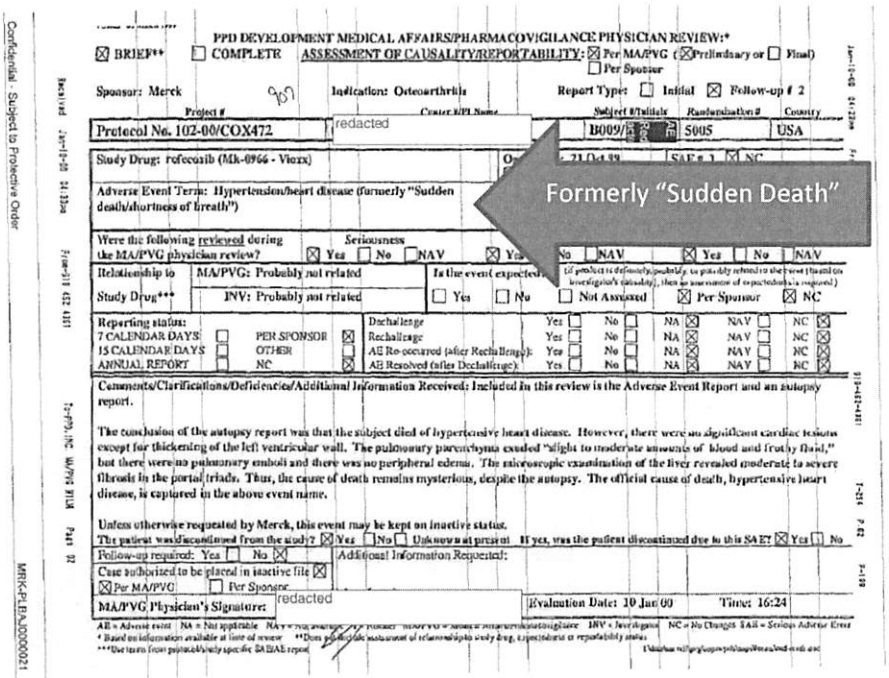
36. The treating doctor of patient number 5005 diagnosed her with having died from "Sudden Death" (a cardiac death):



37. Merck contacted the investigator and had him change "Sudden Death" to "HYPERTENSION /Heart Disease." Later Merck had the entire form re-written, eliminating the initial diagnosis. This transformed case 5005, a study patient treated with Vioxx, from a cardiac death to a non-cardiac death:


ROFECOXIB 25 MG Q.D. VS. NAPROXEN 500 MG B.I.D.
SERIOUS ADVERSE EXPERIENCE
SAE
"Sudden Death" removed
DEATH
COMMENTS
Clinical Development – U.S. Human Health
Merck & Co., Inc
Investigator Name:
Confidential - Disclosure to Unauthorized Persons Forbidden by Order of the Court
MRK-0142011573
MK-0966 Prot. 107, IN 5005 15 of 45

Merck never produced the original, unadulterated adverse event form with "Sudden Death," although they clearly had it at one point in time. The following ASSESSMENT OF CAUSALITY/REPORTABILITY form states that the original adverse event was "Sudden Death/shortness of breath":


PPD DEVELOPMENT MEDICAL AFFAIRS/PHARMACOVIGILANCE PHYSICIAN REVIEW:*

☒ BRIEF** ☐ COMPLETE ASSESSMENT OF CAUSALITY/REPORTABILITY: ☒ Per MA/PVG (☒ Preliminary or ☐ Final) ☐ Per Sponsor

Sponsor: Merck Indication: Osteoarthritis Report Type: ☐ Initial ☒ Follow-up # 2

Project #	Center #/PI Name	Subject #/Initials	Randomization #	Country
Protocol No. 102-00/COX472	redacted	B009/	5005	USA

Study Drug: refecoxib (MK-0966 - Vioxx) ... SAE # 3 ☒ NC

Adverse Event Term: Hypertension/heart disease (formerly "Sudden death/shortness of breath")

Formerly "Sudden Death"

Were the following reviewed during the MA/PVG physician review? ☒ Yes ☐ No ☐ NAV ... Seriousness ... ☐ No ☐ NAV ☒ Yes ☐ No ☐ NAV

Relationship to Study Drug*** MA/PVG: Probably not related / INV: Probably not related ... Is the event expected? ☐ Yes ☐ No ☐ Not Assessed ☒ Per Sponsor ☒ NC

Reporting status:			Dechallenge	Yes	No	NA	NAV	NC
7 CALENDAR DAYS	☐	PER SPONSOR ☒	Rechallenge	Yes ☐	No ☐	NA ☒	NAV ☐	NC ☒
15 CALENDAR DAYS	☐	OTHER ☐	All Re-occured (after Rechallenge):	Yes ☐	No ☐	NA ☒	NAV ☐	NC ☒
ANNUAL REPORT	☐	NC ☒	All Resolved (after Dechallenge):	Yes ☐	No ☐	NA ☒	NAV ☐	NC ☒

Comments/Clarifications/Deficiencies/Additional Information Received: Included in this review is the Adverse Event Report and an autopsy report.

The conclusion of the autopsy report was that the subject died of hypertensive heart disease. However, there were no significant cardiac lesions except for thickening of the left ventricular wall. The pulmonary parenchyma exuded "slight to moderate amounts of blood and frothy fluid," but there were no pulmonary emboli and there was no peripheral edema. The microscopic examination of the liver revealed moderate to severe fibrosis in the portal triads. Thus, the cause of death remains mysterious, despite the autopsy. The official cause of death, hypertensive heart disease, is captured in the above event name.

Unless otherwise requested by Merck, this event may be kept on inactive status.

The patient was discontinued from the study? ☒ Yes ☐ No ☐ Unknown at present If yes, was the patient discontinued due to this SAE? ☒ Yes ☐ No

Follow-up required: Yes ☐ No ☒ Additional Information Requested:

Case authorized to be placed in inactive file ☒ ☒ Per MA/PVG ☐ Per Sponsor

MA/PVG Physician's Signature: redacted Evaluation Date: 10 Jan 00 Time: 16:24

AE = Adverse event NA = Not applicable ... INV = Investigator NC = No Change SAE = Serious Adverse Event

* Based on information available at time of review **Does not include assessment of relationship to study drug, expectedness or reportability status

***Derived from protocol-defined specific SAE/AE term

Confidential - Subject to Protective Order

MRK-PLE0000021

39. Merck personnel discussed this case and the alterations. Eliminating case 5005 obliterated the statistical significance of the increase in heart attacks in this particular study.

40. Dr. Reicin, the head of the clinical trial asked Dr. Barr (Merck cardiologist) to change his diagnosis of case 5005:

Barr to Reicin November 8, 2000 11:43 AM

"Alise, in follow-up to our conversation, I classified the "Hypertensive Heart Disease" patient is [sic] clinically a case of Sudden Cardiac Death in ADVANTAGE AN5005:

This is a 73 yo woman with an SAE of "Hypertensive Heart Disease". The WAES report states that she [sic] has had HTN & Hyperlipidemia. She was not [sic] treated with any cardioactive [sic] meds. She called her son with shortness of breath and when her son arrived at the patient's home, he found that she had died. A postmortem called the COD to be hypertensive heart disease.

Common things being common, the clinical scenario is likely to be MI. Certainly, it is not definitive. I just used my clinical judgment. If it is easier to call this an unknown cause of death, I could be persuaded to say that as well."[40]

41. Reicin then "persuaded" Barr to change his diagnosis to one that would exclude the patient from the MI category.[40]

Reicin to Barr November 8, 2000 12:01 PM

"I think this should be called an unknown cause of death--the committee would not have said this was an MI and I think this is the best way to go since it leaves the process in place. The overall numbers stay the same but the term changes. To confirm was this included in the MI only analysis or not? (hopefully not)."

Barr to Reicin November 8, 2000 12:58 PM

"The definition that the adjudicators used was (direct quote of the Adjudication SOP):

Sudden Death and/or Unexplained Death:

"Sudden and/or unexplained death is defined as witnessed instantaneous or near-instantaneous [sic] death that occurs without warning or within one hour of non-diagnostic symptoms, or as an unwitnessed, unexpected death in which criteria for fatal coronary or cerebrovascular [sic] event are not met.

I have two concerns: first, it probably would have been wise to adjudicate all Deaths associated with any CV terms because unknown causes of death are part of the definition above. Second, I disagree that the committee would not have called AN 5005 a Sudden Death and/or Unexplained Death. They may have (or maybe not), but I would not be definite."

42. Reicin responded:

Reicin to Barr November 11, 2000 18:35 PM

"At this point it is too late to reverse what has been done. Deborah said that you told her to count this as an MI I don't [sic] think the adjudication committee would have counted this as an MI.

"Since the APTC analysis does not change whether we call it unknown cause of death or sudden death I would prefer unknown cause of death so that *we don't [sic] raise concerns*. I still strongly feel that this should not be an MI-- how do you know it wasn't [sic] a massive stroke, primary arrhythmia? [sic] pulmonary embolus etc." [Emphasis added] [40]

43. The FDA reviewed case 5005 and concluded it was sudden cardiac death. More importantly the patient presented with unstable angina (chest pain that resulted in a heart attack):

Of note, the cause of death for patient # 065 5005 (on rofecoxib), had been listed by the investigator as hypertensive heart disease and not referred for adjudication as a potential cardiovascular thrombotic event to the cardiovascular adjudication committee. The patient called her son complaining of chest pain and by the time the son arrived she was dead. In the opinion of this medical reviewer, the cause of death for this patient was sudden death, which would in fact meet criteria for cardiovascular thrombotic event. [Italics in original] MRK-PUBLIC0000371

44. Eliminating case 5005 abolished the statistical significance of the increase in heart attacks in this study. Merck never changed the diagnosis pursuant to FDA review and this case was never classified as unstable angina so an analysis of Merck data would not have counted this as a Vioxx related case of unstable angina.

45. There is other evidence of Merck manipulation of patient data that made Vioxx look safer than it was. **As I testified at deposition, due to Merck's manipulation of data, the only way to analyze Merck's data is to obtain the original medical records.** Merck has never produced.

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22 A. Well, except for the -- except for the ones, 23 the APPROVe is seven to four. But remember that -- that 24 of those events, there are, I'm sure, more unstable 25 angina events that are classified in that study as MI's.

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1 Someone has unstable angina, they have an MI, they get 2 classified as an MI. 3 Because you only get -- this is for sure. Per 4 event, you only get one diagnosis, and if you have 5 unstable angina and MI, they are not going to write down 6 unstable angina. Or if you have unstable angina and 7 sudden death, they are not going to write down unstable 8 angina. So for sure there are more cases. 9 But have to go back to the medical record. I 10 am not even sure you can get that because it didn't come 11 out in the adjudication procedure as far as I know. 12 They wouldn't get the medical records that would show 13 the unstable angina.

46. The editors of the New England Journal of Medicine (NEJM) wrote an unprecedented critique of Merck's manipulation of data:

"In addition, the memorandum of July 5, 2000, contained other data on cardiovascular adverse events that we believe would have been relevant to the article. We determined from a computer diskette that some of these data were deleted from the VIGOR

manuscript two days before it was initially submitted to the *Journal* on May 18, 2000. Taken together, these inaccuracies and deletions call into question the integrity of the data on adverse cardiovascular events in this article. We have asked the authors to submit a correction to the *Journal.*" - Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8. Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

What Merck claims that I said	**What I actually said**
"He did not review any of the data on unstable angina, not because they were unavailable..." (id. at 147:25-148:13)"	Q. My question for you is, can you identify, as you sit here today, a specific randomized, controlled trial that you believe to show a statistically significant increased risk of unstable angina in association with the use of Vioxx? A. I think it's probably in some of the larger trials. **But in order to get the answer, we have to go out and re—redo the data that Merck did because of the way Merck conflated the tables. In other words, if you had unstable angina MI, you were categorized as MI. So you would have to actually go back to the patient charts and get the data.** I think that's probably doable. I don't think that's necessary.
..., but because he simply chose not to (id. at 154:1 1-17)."	Q. For purposes of developing your own opinions in this case with respect to the potential question that-- of whether Vioxx is causally associated with an increased incidence of unstable angina, did you, yourself try to pool together data from various studies and perform any kind of statistical analysis? A. **No, just asking Madigan to do it on your data.** You have got the best data. I mean, you have the most data on - you have all the Vioxx placebo trials. They are all yours. So that's the only data set that exists that it can be done on. He's got the data.

47. I also provided the results of Dr. Madigan's analysis:

Madigan ACS analysis

1.621 (1.167, 2.252) p=0.004

by ACS (MI, unstable angina, SD) Vioxx vs placebo

Not including cardiac arrest it is 1.53 (1.09, 2.15) p=0.013

The CVT endpoint across the three 203 studies.

On drug IR is 1.82 (1.22, 2.71), p=0.003. Adjudicated is also SS:

48. During the relevant time frame the ICDA-9 code for ACS was the same as for unstable angina, 411.1. Thus epidemiologic research results, which are usually based on ICDA coding, would not distinguish between these two diagnoses.

49. Finally, this is not, as Merck has suggested, a composite or "fruit salad" case. A more appropriate analogy is skin redness that precedes a sunburn. Everyone who gets a sunburn is exposed to UV light which first causes inflammation and skin irritation (redness) (akin to angina). Everyone with red skin from UV exposure does not develop a burn, but all sunburns go through a phase of skin irritation. In this case, if someone suffered a sunburn (heart attack). Merck did not record their skin irritation (angina).

50. Merck cited Dr. Madigan's alleged support for the fruit analogy however he said that he was not an expert of this issue:

Do you agree with the following
23 statement: A meta-analysis that relies on a composite
24 cardiovascular endpoint could not detect risk in a
specific cardiovascular subcategory since any risk in
one subcategory might be offset by either a higher or a
lower risk in another subcategory?
A. Sure, I agree with that. It's a --
you're kind of asking the wrong person as to which
where is the right level of specificity to be
conducting such an analysis.

Q. You agree with that statement?
A. I said yes, yeah. And I know what
you're getting at, but there are -- you know, I guess
there are different types of unstable angina for all I
know, you know. So where should you -- where do you
want to be when you're posing a clinical question.

These are clinical questions. It's not -- it's outside my range of expertise.

Q. Still yes to my question, correct?
A. Yeah, but with the caveat that I'm not, you know --
Q. You're not a clinician?
A. I'm not a clinician. It's not up to me to decide what the right endpoint is or the right granularity of the endpoint. I don't do that.
Q. You're relying strictly on David Egilman for that?
A. Exactly.

Under penalties of perjury, I declare that I examined this affidavit and to the best of my knowledge and belief, it is true, correct and complete.

March 16, 2017

David Egilman MD, MPH

_____
Date

David Egilman